REMARKS/ARGUMENTS

The Pending Claims

Claims 35, 39-42, 45-48, 52, and 53 are pending and are directed to a method of changing the sensory perception of an animal.

Discussion of Obviousness Rejection

Claims 35, 39, 40, 41, 42, 45-48, 52, and 53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of U.S. Patent 6,838,444 (Zoghbi et al.), U.S. Patent 5,837,511 (Falck-Pedersen et al.), U.S. Patent 6,913,922 (Bout et al.), and Wigand et al., *Arch. Virol.*, 64(3): 225-233 (1980), alone or in view of (a) U.S. Patent 6,821,775 (Kovesdi et al.), (b) Staecker et al., *Otolaryngol. Head Neck Surg.*, *119*(1): 7-13 (1998), (c) U.S. Patent 6,455,314 (Wickham et al.), and/or (d) Mizuguchi et al., *Gene Ther.*, *9*(12):769-776 (2002). These rejections are traversed for the reasons set forth below. The substance of the rejection is set forth in the Office Action and is not repeated herein.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on the following factual inquiries: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Regarding the scope and content of the prior art, Zoghbi et al. teaches a method of generating hair cells in a mammal using the genus of adenoviral vectors to deliver an atonal-associated nucleic acid. The Falck-Pedersen patent discloses methods for generating replication-deficient non-group C adenoviral vectors (i.e., subgroups A, B, D, E, and F). The Bout patent discloses that different adenovirus serotypes exhibit different tropisms. For example, the Bout patent discloses that adenovirus serotypes 2, 4, 5, and 7 have a natural

tropism for lung epithelia and other respiratory tissues, while serotypes 40 and 41 have a natural tropism for the gastrointestinal tract. The Bout patent also discloses replication-deficient adenoviral vectors based on serotype 35 or 11, or chimeric vectors comprising a portion of the Ad35 or Ad11 genome. The Wigand reference discloses the isolation of a serotype 36 adenovirus (Ad36), which is characterized as belonging to subgroup D. The Wigand reference discloses that Ad36 is distinct both in neutralization and hemagglutination-inhibition from all other human adenoviruses, and exhibits a unique DNA restriction pattern. The Wigand reference also discloses that the DNA structure of Ad36 is closely related to Ad28 and other subgroup D adenoviruses.

The Kovesdi patent discloses an E1/E3/E4-deficient serotype 5 adenoviral vector encoding a pigment epithelium-derived factor (PEDF). The Staecker reference discloses a method of transfecting auditory hair cells with an HSV vector encoding brain-derived neurotrophic factor. The Wickham patent discloses recombinant adenovirus fiber proteins that are modified to reduce affinity for the CAR cellular receptor. The Mizuguchi reference discloses adenoviral vectors that are ablated for binding to CAR and αv-integrin, as well as adenoviral vectors containing the RGD peptide inserted into the HI loop of the fiber knob.

For the sake of argument and for purposes of the present analysis, one of ordinary skill in the art can be assumed to be someone with an advanced degree in a relevant field and a few years of experience in the relevant art.

The method defined by the pending claims comprises administering to the inner ear a serotype 28 adenoviral vector (Ad28) comprising a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, such that the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

The Office Action confirms that each of the Zoghbi, Falck-Pedersen, and Bout patents does not explicitly teach a method of changing sensory perception in an animal by administering the specifically selected adenoviral vector recited in the pending claims, namely an Ad28 vector comprising Hath1. Indeed, based on the combined disclosures of the Zoghbi, Falck-Pedersen, and Bout patents, the Office Action states that one of ordinary skill in the art would not have been motivated to select a subgroup B, C, E, or F adenoviral vector

to deliver a gene to the supporting cells of the inner ear. In view of the disclosure of the Wigand reference, however, the Office Action concludes that one of ordinary skill in the art would have been motivated to use an adenoviral vector based on serotype 28 based on its similarity to Ad36.

Contrary to the assertions of the Office Action, one of ordinary skill in the art would not have had a credible reason to choose Ad28 for use in the context of a method such as described by the Zoghbi patent with a reasonable expectation of success based on the disclosure of the Wigand reference. In this regard, while the Wigand reference discloses that the genomes of Ad36 and Ad28 are similar, the Wigand reference also states that Ad36 is genetically similar to other subgroup D adenoviruses. There is nothing in the Wigand reference that would have provided a reason for one of ordinary skill in the art to have specifically selected Ad28 from among the more than 20 serotypes within of subgroup D, much less from among the 51 adenoviral serotypes known in the art. Moreover, one of ordinary skill in the art at the time of the present invention would have known that Ad36 infects cells of adipose tissue (see, e.g., Dhurandhar et al., *Int. J. Obes. Relat. Metab. Disord.*, *24*(8): 989-996 (2000), and Dhurandhar et al., *Int. J. Obes. Relat. Metab. Disord.*, *25*(7): 990-996 (2001)). Thus, if anything, one of ordinary skill in the art at the time of the claimed invention would have been led away from using Ad36 to transduce cells of the inner ear. Likewise, using the Office's reasoning, the art available at the time of the claimed invention also taught away from using Ad28 to transduce inner ear cells.

Furthermore, selecting an adenovirus of a specific serotype from a given subgroup is not simply a matter of "routine optimization," as alleged in the Office Action. According to M.P.E.P. § 2144.05, "differences in *concentration or temperature* will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical" (emphasis added). M.P.E.P. § 2144.05 further states that "a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that *one skilled in the art would have expected them to have the same properties*" (emphasis added). The selection of a distinct organism (i.e., an adenovirus of a particular serotype) from among a group of related but different organisms (i.e., an adenovirus subgroup) is much different than the routine adjustment of the conditions of a particular chemical reaction or process. While adenoviruses

of different serotypes within the same subgroup share structural similarities, such adenoviruses are different enough that one of ordinary skill in the art would not expect adenoviruses within a particular subgroup to have the same properties.

The Office Action also states that the results described in the previously filed Rule 132 declarations are "exactly as expected" in view of the prior art (Office Action at page 21, third complete paragraph), given that non-subgroup C adenoviral vectors were developed to overcome technical difficulties associated with subgroup C adenoviral vectors (i.e., Ad5). The Office provides no evidence to support the allegation that non-subgroup C adenoviral vectors were developed solely to overcome technical difficulties associated with subgroup C adenoviral vectors. The "issues" referred to by the Examiner and referenced in the teachings of Falck-Pedersen relate to immune responses to Ad5 vectors. Whether a non-group C adenovector is more or less likely to trigger a host immune response is entirely irrelevant to the unexpected properties described in the previously filed Rule 132 declaration. The prior Rule 132 declaration teaches that one of ordinary skill in the art would not have expected a non-subgroup C vector to **transduce inner ear cells more efficiently** than subgroup C vectors simply because the non-subgroup C vector is not of subgroup C. Thus, the claimed vector, indeed, has unexpected properties (transduction efficiency) relative to Ad5 vectors that were not predictable from the prior art references cited by the Examiner, whether considered alone or in the aggregate. The results discussed in the previously filed Rule 132 declarations are unexpected in that human cells appear to have reduced innate immunity against Ad28 as compared to Ad5, which enhances the therapeutic efficacy of Ad28 vectors in inner ear cells.

Nothing in the prior art, including the secondary references cited by the Office Action, discloses or suggests a serotype 28 adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, much less a method of using such an adenoviral vector to change the sensory perception of an animal. Therefore, the prior art in its entirety, including the combination of cited references, does not disclose or suggest the subject matter defined by the pending claims.

Considering all of the Graham factors together, particularly the fact that the combination of the cited references do not disclose or suggest all of the elements of the pending claims, and that the claimed invention involves surprising and unexpected results, it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of cited references. Accordingly, the obviousness rejections under Section 103 should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,

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